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10/588,176	08/02/2006	Paul Adriaan Van Der Schaaf	LS/95-23017/A/PCT	5060

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EXAMINER	
SHTERENGARTS, SAMANTHA L	
ART UNIT	PAPER NUMBER
4131	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,176	VAN DER SCHAAF ET AL.	
	Examiner	Art Unit	
	SAMANTHA SHTERENGARTS	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36 and 38* is/are pending in the application.

4a) Of the above claim(s) *3-20,27-32 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,21-26 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36 and 38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *26 December 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the reply filed on February 4, 2008 is acknowledged. The requirement is still deemed proper and is therefore made final. Currently, claims 1-36 and 38 are pending in the instant application.

2. Claims 3-20, 27-32, and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected subject matter. Claims 1-2, 21-26, and 33-36 read on an elected invention and are up for consideration in the instant application.

Priority

3. The instant application is a national stage entry of PCT/EP05/50362, filed January 28, 2005; which claims priority to U.S. Provisional Application 60/543,107, filed on February 9, 2004.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on December 26, 2006 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is enclosed herewith.

Claim Rejections - 35 USC § 112

(First Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. **Claims 1 and 2** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The nature of the invention is a crystalline polymorph form A of Zolmitriptan, pharmaceutical compositions containing these forms, and methods of preparation. The state of the prior art is that the most useful method to compare X-ray powder diffraction data is to overlay and align the respective films and plots. The ensuing comparisons of peak positions and intensities will show whether the structures are the same or different (Byrn page 63). An x-ray diffraction pattern is like a "fingerprint" and Applicant has not provided why the certain peaks found in claims 1 and 2 are the only required peaks in the x-ray diffraction pattern that must match. There is no description found in the specification why these certain claimed peaks are the only peaks required. The peaks present in the claims do not include all peaks of the x-ray diffraction pattern. The amount of direction present in the specification is the x-ray diffraction patterns of the claimed crystalline forms. Applicant has not provided why the entire "fingerprint" is not being claimed, nor does Applicant provide why only certain peaks are found in the claims and not others. The claims to only certain peaks do not find written description in the specification as the claims do not include the "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of the claimed forms and why the entire "fingerprint" is not required. While there is some description for characteristic peaks found

on pages 2 and 3, there is no written description provided as to why these peaks are considered characteristic. Therefore, claims 1 and 2 are rejected as there is no written description as to why the data present is the only data required from the "fingerprints" to distinguish the claimed forms from other forms.

6. **Claim 22** is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The nature of the invention is a method of preparation of crystalline polymorph A. The state of the prior art is that the mixing of organic solvents, especially with reactions of composition, there is a rearrangement of bonds that takes place. "This process is determined by such high equilibrium constant that it is possible to consider the process as practically irreversible" (Wypych, pg. 508, section 9.2.6). In claim 22, Applicant has not made clear whether the organic solvent is selected from a sulfoxide OR amide or from a sulfoxide AND amide mixture. In the former case, the specification does contain written description to support using a sulfoxide as an organic solvent and using an amide as an organic solvent. However, the specification does not support using a mixture of the two. A mixture of organic solvents, such as in the instant case, is not disclosed in the specification and one of ordinary skill in the art would have no reason to expect successful or unexpected results from a process of crystallization using a mixture of these two solvents. Therefore, claim 22 is rejected as there is no written description disclosing a mixture of these two organic solvents in the process for preparing a crystalline polymorph A of Zolmitriptan.

(Second Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 23, 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 23, wherein the solution additionally contains a non-solvent selected from alkanes and ethers. The word "non-solvent" renders the claim indefinite because it is unclear to a person of ordinary skill in the art what "non-solvent" means. There is no definition in the specification, and claim 23 discloses alkanes and ethers as "non-solvents;" however, alkanes and ethers are generally used as solvents or solvent mixtures in the chemical arts. (See Handbook of Solvents, Wypych, section 3.3.1 on hydrocarbons and 3.3.9 on ethers).

Instant claims 35 and 36 are directed to a pharmaceutical composition comprising a crystalline polymorphic form (claim 35) and Zolmitriptan containing a crystalline polymorphic form (claim 36). The phrase "crystalline polymorphic form" renders the claim indefinite because it does not clearly set forth the metes and bounds which are being sought to be protected by the patent. The phrase "crystalline polymorphic form" is interpreted as *any* polymorphic form of this particular crystal. Without any further limitation in the claims, Examiner cannot determine which crystalline polymorphic form Applicant regards as his invention, or how this indefinite polymorphic form is different from Zolmitriptan as patented in Patel (U.S. Patent 6,804,103).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-2, 25-26, and 35-36 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Patel (U.S. Patent No. 6,084,103).

Instant claims 1 and 2 are directed to a crystalline polymorph A of formula (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone (chemical name for Zolmitriptan) with a certain X-ray powder diffraction pattern and peak intensity as claimed. Patel teaches the preparation of (S)-4-{3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl}-2-oxazolidinone in Example 1, Stage 6A. In Polymorphism in Pharmaceutical Solids, Brittain discloses the difficulties with x-ray diffraction. "X-ray diffraction studies of crystals have been achieved at 100K, well below (by more than 200K) the temperature range of thermodynamic stability. There are several documented examples of the inability to obtain a previously prepared crystal form." Due to the imperfections known in the art that are associated with measuring peak intensity due to equipment experimental error and impurities, Examiner cannot ascertain that crystalline polymorph A of Zolmitriptan is any different from the Zolmitriptan compound form claimed in Patel due to their similar procedure of preparation.

Instant claim 25 is directed to a process of preparing a crystalline polymorph A of (S)-4-{3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl}-2-oxazolidinone wherein crystalline Zolmitriptan is suspended, or amorphous Zolmitriptan is dispersed, in an organic solvent,

provided that the organic solvent does not contain 1-butanol, anisole, ethyl methyl ketone, tetrahydrofuran, or 1,4-dioxone. Patel teaches, (Example 1, Stage 6A, columns 12 and 13, lines 59 and 2 respectively), the use of ethyl acetate as a solvent, as well as the chilling of the suspension. At the end of the procedure, when the solvent is distilled off and the suspension is cooled and then dried, the process of crystallization is occurring, prior to the purification of the product.

Instant claim 26 discloses a process of claim 25 wherein the organic solvent is an alcohol or an acetate. As discussed above in the rejection of claim 25, the organic solvent is ethyl acetate as taught in Patel (Example 1, Stage 6A, column 12, line 59).

Instant claim 35 discloses a pharmaceutical composition comprising the crystalline polymorphic form of Zolmitriptan and a pharmaceutically acceptable carrier. As Brittain discloses in Polymorphism in Pharmaceutical Solids, (pg. 28) "For the specific instance of polymorphic systems, the substance itself will ordinarily be the only component present. The situation complicates for solvates or hydrates since the lattice solvent will comprise a second component. Hydrate/solvate systems cannot be systems of one component, since the different phases will not have the same composition." The only component present in the polymorph is the crystal lattice. Once hydrated, as in the case when a carrier is added, a second component will change the equilibrium and ultimately the composition of the crystalline polymorph form of the compound. By placing the crystalline polymorph form A of Zolmitriptan in a carrier to yield a pharmaceutical composition, it would actually rehydrate the polymorph resulting in a loss of form, and ultimately yielding the Zolmitriptan compound as disclosed in Patel (claim 1, formula 1). **Instant claim 36** discloses Zolmitriptan containing a crystalline polymorphic form according

to claim 1. As stated above in the rejection of claim 1, Examiner cannot differentiate between Zolmitriptan and the Zolmitriptan crystalline form based on the compound characteristics provided. Patel teaches Zolmitriptan by the chemical name of (S)-4-{3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl}-2-oxazolidinone in claim 1, formula I.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 21-24 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel (U.S. Patent No. 6,084,103), and further in view of Armarego et al (Purification of Laboratory Chemicals (4th Edition), 1997, Elsevier) and Brittain, Harry, G. Polymorphism in Pharmaceutical Solids. V. 95. New York: New York Marcel Dekker, Inc., 1999.

Determination of the scope and contents of the prior art

Patel, process for preparing crystalline polymorph A of formula (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone (chemical name for Zolmitriptan) (Example 1, Stage 6A). Armarego et al. (Purification of Laboratory Chemicals (4th Edition), 1999, Elsevier. pg. 12,13, 56), Processes of recrystallization and purification and suitable solvents.

Ascertaining the differences between prior art and instant claims

Instant claim 21is directed to a process for preparing crystalline polymorph A of formula (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone wherein a solution of Zolmitriptan in an organic solvent or mixture of organic solvents is cooled, provided that the solution does not contain 1-butanol, anisole, 2-propanol, ethyl methyl ketone, tetrahydrofuran, 1,4-dioane, or ethyl acetate.

Patel discloses a process for the preparation of (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone in Example 1, Stage 6A, where a solution of the aforementioned chemical is made using a similar process as with the instant claim, but employing ethyl acetate in the crystallization step, and employing 10% ethanol in ethyl acetate in the purification step. Armarego et al. (pg. 12-13) discloses a general method for recrystallization and purification on pg. 12, and later discloses a guide on choosing appropriate solvents on pg. 13. The section on "Choice of Solvents" discusses the best solvents for use in recrystallization. Ethyl acetate, as employed in prior art Patel fits all of the characteristics (a)-(f) for a good solvent choice in recrystallization. In the second section under "Choice of Solvents," (a) discloses the use of lower

alcohols such as methanol and ethanol (pg. 13) and methanol is also disclosed on pg .12 under the “Techniques in Recrystallization" section. These lower alcohols are very closely related in chemical and physical characteristics to butanol and propanol. Therefore, in the recrystallization process, one of ordinary skill would expect success with these organic solvents, and the exclusion of ethyl acetate, 1-butanol, and 2-propanol, in this process, would not produce any novel results to motivate one to exclude them.

Instant claim 22 is drawn to the process of claim 21 wherein the organic solvent is selected from C_1-C_4 alkanols, sulfoxides and/or amides, or mixtures of C_1-C_4 alkanols with water. As discussed above in the rejection of claim 21, Armarego et al. discloses the use of alkanols or alkanol mixtures with water as excellent solvents for recrystallization purposes on pg. 13, under "Choice of Solvents" section.

Instant claim 23 is drawn to the process of claim 21, wherein the solution additionally contains a non-solvent selected from alkanes and ethers. As described on pg. 12 of Armarego et al., for materials being crystallized that have lower melting points, it is sometimes convenient to use dilute solutions in acetone, methanol, pentane, and ethyl ether. Therefore, ethers can be used to dilute solutions in addition to their use a common organic solvents in recrystallization processes.

Instant claim 24 is drawn to the process of claim 21, in which the solution is cooled from a temperature of about 20°C to 100°C down to about –20°C to 10°C. Patel discloses a process for the preparation of (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone in Example 1, Stage 6A where in line 59, the compound is extracted at about 50°C using ethyl acetate and in the next column in line 2, he further discloses that the suspension is chilled to about 5°C to complete the crystallization process.

Instant claim 33 is directed to the process according to claim 21 wherein seeding is carried out with crystals of the desired crystalline polymorph. It is well-known in the art that seeding a small piece of a single crystal material from which a large crystal comes from will grow a larger crystal by dipping the seed into a supersaturated solution and cooling. Additionally, Brittain (pg. 188) discloses, "If crystals do not grow as expected from a saturated solution, the interior of the vessel can be scratched with a glass rod to induce crystallization by distributing nuclei throughout the solution. Alternatively, crystallization may be promoted by adding nuclei, such as seed crystals of the same material." The process of seeding is obvious to one of ordinary skill in the art. The common employment of seeding in crystallization can also be found in Armarego et al. (pg. 56, line 4).

Instant claim 34 is directed to the process according to claim 21 in which the solution or dispersion of Zolmitriptan is prepared in situ. In situ, in its chemical meaning, is defined as "in the reaction mixture" or "procedures that are performed in place." Patel discloses the in situ preparation of the solution of (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone (Zolmitriptan) in Example 1, Stage 6A. The compound is not dried vacuum dried until the final step before purification, during the centrifuging of the crude product. This step can be alternatively accomplished in situ, as seen in Patel (claims 12-20) where the process of preparing (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone does not involve the in vacuo drying of the compound, or the isolation of the compound.

Resolving the level of ordinary skill in the pertinent art – Prima Facie Case of Obviousness

One of ordinary skill in the pertinent art would be motivated to combine the sources of Patel along with the disclosure of Armarego et al. due to their common discussion of crystallization of organic compounds and common techniques employed during these processes. One of ordinary skill would be motivated to make the necessary modifications to arrive at the instant invention with reasonable expectation of success for obtaining a compound of formula (S)-4-[[3-[2-(diemthylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone.

Thus, the instant claims are *prima facie* obvious over the teachings of the prior art.

Conclusion

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samantha Shterengarts whose telephone number is (571)270-5316. The examiner can normally be reached on Monday thru Thursday, 9AM – 6PM Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang and Janet Andres can be reached on 571-272-0562 and 571-272-0867, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAMANTHA SHTERENGARTS/
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